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IN THE CANADIAN PCT RECEIVING OFFICE

In re Application of:

Applicant: **Canadian Blood Services et al.**

Filed: **February 7, 2005**

Serial No.: **PCT/CA2005/000250**

Title: **A METHOD FOR THE SIMULTANEOUS DETERMINATION OF BLOOD GROUP AND PLATELET ANTIGEN GENOTYPES**

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AMENDMENT/RESPONSE UNDER ARTICLE 34 PCT

Sir:

In response to the Written Opinion mailed June 15, 2005, please amend the application as follows:

In the Specification

Please replace pages 20, 21, 26, 27, 29 and 37 originally filed in this application with amended pages 20, 21, 21a, 26, 27, 29 and 37 attached hereto. Please also the pages of Appendix A with new pages 50 to 70 of Appendix A as enclosed to include page numbering. In addition, please insert new pages 1 to 9 of the Sequence Listing into the specification following the claims.

In the Claims

Please replace claim pages 71 to 78 originally filed in this application with amended claim pages 71 to 76 attached hereto.

REMARKS

By way of this amendment under Article 34 of the PCT, Applicant respectfully submits that pages of the specification are herein amended to correct clerical errors

appearing therein. In particular, amended pages 20, 21, 21a, 27 and 29 are herein provided to make accurate reference to SEQ ID NOs. of the Sequence Listing corresponding to the sequence appearing therein. Page 26 is herein amended to correctly identify the primer names corresponding to antigen GYPBS/GYPBs in Table 1 as GYPBe4S and GYPBe4A. In addition, page 37 is herein amended at lines 24 to 27 to clarify which symbols are intended to correspond to the colours referenced in Figures 1 and 4. Applicant notes that this clarification is necessary as the figures of the application are provided in black and white and not colour. The clarifying amendments in this regard find support in the legends of Figures 1 and 4 respectively.

Furthermore, amended pages containing the data of Appendix A are also enclosed to provide the appropriate page numbering.

Sequence Listing pages 1 to 9 are also enclosed for insertion in the present application following the claims. The Sequence Listing pages as provided are identical to those submitted on May 12, 2005 in accordance with the Sequence Listing provided in compliance with WIPO Standard ST 225 Form PCT/ISA/225 mailed April 13, 2005. Applicant respectfully requests that the pages of the Sequence Listing be inserted into the present application.

Concerning the claims of the present application, the Examiner alleges that claims 1 to 5, 8 to 10, 12, 28 to 33, 40 to 42 and 45 lack novelty in view of the teachings of document D1. Additionally, the Examiner believes that the novelty of claims 1 to 5, 8 to 12 and 40 are negated by the teachings of document D2. Applicant points out that the teachings of D1 are restricted to a PCR methodology and primers having specificity to a single SNP of only one blood group antigen, that being RhD. Alternatively, the present invention is directed to a multiplex PCR methodology and products for conducting the same for identifying and analyzing a plurality of blood group and platelet antigens simultaneously. The mere disclosure of a single primer having similarity to a primer of the present invention does not negate the novelty of the present methodology and products thereof, for achieving a very different and more complex multiplex PCR assay. In particular, Applicant asserts that the subject matter of original claim 12, now claim 7, was not previously disclosed in either D1 or D2. Neither D1 nor D2 disclose an

oligonucleotide primer and probe set for analyzing a plurality of SNPs simultaneously. That is, an oligonucleotide primer and probe set suitable for use in multiplex PCR detection of blood group or platelet antigens is not disclosed, regardless of the preferred SNP selected from the group provided. Applicant understands the teachings of D1 to disclose specific PCR primers relevant to the identification of RHD SNPs, namely ga41 and ga42 and re94. Applicant submits that ga41 and ga42 are very different from the RHD exon 4 primers of the present invention (Table 1). Furthermore, D1 provides no evidence that these primers would be useful for the simultaneous determination of RHD SNPs. In respect of Re94, according to the teachings of D2, this primer does possess similarity to a single primer of the present invention, namely RHDe9A (as aligned herein below):

Re94	CTT GGT CAT CAA AAT ATT TAG CCT
RHDe9A	TT GGT CAT CAA AAT ATT TAG CCT C

However, the sense primer is very different and therefore, their paired usefulness in the simultaneous determination of a plurality of blood group or platelet antigen SNPs is not taught in D1.

Applicant submits, however, that claims 1 to 11 are herein amended as claims 1 to 6 and are now more clearly directed to preferred nucleic acid sequences and oligonucleotide sets of the present invention for use in multiplex detection analysis of a plurality of blood group or platelet antigen SNPs. In doing so, claims 9 and 10 are deleted, without prejudice in an effort to obtain a favourable IPRP. Objected claims 28, 29, 32 and 40 are also deleted by way of this amendment. Remaining claims 30 and 31 (renumbered as claims 24 and 25) now depend on claim 9 as herein provided. Amendment is also herein provided to objected claims 33 and 41 (now claims 23 and 32) to clarify that the claimed methodologies encompass the simultaneous analysis of a plurality of blood group or platelet antigen specific SNPs, and include the use of a plurality of primers as defined in Table 1.

Applicant extends the preceding comments and related amendments in argument to the objections to novelty in view of D2. Applicant submits that the teachings of D2 relate

to primers for the amplification of HPA-1a/b SNP. The antisense primer PLA2-1 is very similar to GP3Ae3A.

PLA2-1	TT CTG ATT GCT GGA CTT CTC TT
GP3Ae3A	ATA GTT CTG ATT GCT GGA CTT CTC

Again, the sense primer is different and therefore their paired usefulness in the simultaneous determination of blood group and platelet genotypes is not disclosed. Accordingly, Applicant believes the claims as herein amended are novel. Furthermore, the subject matter of the present claims is also believed to be inventive, in light of the common difficulties known in the art in overcoming the complexities of PCR multiplexing assays. To this end, Applicant asserts that the present invention is shown to overcome the difficulties of a multiplexing methodology to provide a useful and inventive means for simultaneous detection of a plurality of blood group and platelet antigens in a single reaction vesicle, which has not been previously achieved.

The amendments herein provided to objected claims 28, 29 to 33, 41 and 45 are believed to obviate any further objections to the novelty of the subject matter therein provided. In particular, the subject matter of objected claims 28, 29 and 33 has been effectively combined to provide new claim 23, with an emphasis on the simultaneous identification and analysis of a plurality of blood group SNPs, including the use of a plurality of primers of Table 1.

In particular, Applicant once again emphasizes that the teaching of a method of genotyping a single blood group antigen does not serve to negate a methodology that is optimized to simultaneously identify a plurality of blood group or platelet antigens. D5 is alleged to negate the novelty of claims 33 and 41, as originally filed. Applicant respectively traverses this objection on the basis that D5 does not carry out or disclose primer sequences that are effective in multiplex PCR for determining blood group genotypes. A mere recitation of a set of criteria for designing primers does not direct a person of skill in the art to achieve a reliable, multiplex PCR assay for identifying rare blood group genotypes. However, in the interest of obtaining a favourable IPRP,

Applicant advises that new claims 23 and 32 (formerly claims 33 and 41) have been amended to include specific primers of the present invention. Accordingly, the claims as amended are believed to be novel over the teachings of any of D3 – D7.

Further still, Applicant asserts that the shear convenience provided by the present invention, allowing for a specific and accurate determination of a blood group genotype combats any argument of a lack of inventiveness in the present invention, whereby a convenient, efficient and accurate tool is provided to meet a long standing need in the art of blood screening, for example.

Claims 1 to 5, 8 to 12, 28 to 33, 40 to 42 and 45 have also been objected to as lacking inventive step in view of one or more of the teachings of D3 to D7. Applicant respectfully traverses the basis of these objections. That is, the mere incentive for a person of skill in the art to try to obtain primers to a variety of blood group antigens would not serve to negate the inventiveness of the present invention, which provides novel primers directed to blood group antigens having the capability to perform in a multiplex PCR assay to identify a variety of blood group SNPs, some having specificity to very rare blood groups, simultaneously. Furthermore, these teachings do not describe nor suggest a methodology or primers for use therein for the simultaneous detection of unrelated blood group and platelet genotypes. Applicant asserts that efforts beyond routine experimentation were required to achieve the methodology of the present invention, including the identification and optimization of the primers, as herein claimed. As such, Applicant respectfully submits that a direction by the prior art, either alone or in combination does not lead a person of skill in the art to the subject matter as currently claimed. As amended, Applicant contends that the inventiveness of the subject matter of the current claims is clearly evident.

Several claims of the present application have also been alleged to be indefinite. To this end, Applicant submits that claim amendments as herein provided are provided to more clearly and definitively define the subject matter thereof. In particular, objected claims 12, 14, 17 and 41 are herein amended as new claims 7, 9, 12 and 32 to further define the SNPs as corresponding to a "blood group or platelet antigens genotype". In

addition these claims have been amended where appropriate to define the antigens of interest as "blood group or platelet" antigens. Objected claims 4, 9 and 40 have been deleted by way of these amendments. Claim 24, now claim 19 has been amended to delete the objected terminology as appearing therein. Claim 27, now claim 22 is also herein amended to provide the appropriate antecedent basis. Objected claims 28 and 29 are herein deleted. Claim 34, is herein amended as claim 26 to clarify the terminology therein provided. In addition, the term "preferably" has been deleted from new claims 28, 30 and 31 (corresponding to original claims 36, 38 and 39). New claim 36 is directed to a preferred embodiment of former claim 38.

Applicant respectfully submits that the claims of the present application are both novel and inventive. As such, a favourable International Preliminary Report on Patentability of the claims contained herein is respectfully requested.

Respectfully submitted,

Canadian Blood Services

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software for automated genotype calling. Each of the relevant gene regions are PCR amplified from purified genomic DNA in a single reaction using the following oligonucleotide primer designs:

Gene Primer	Sequence (5' - 3')	
RHD Exon 4	RHDe4S	AGACAAACTGGGTATCGTTGC (SEQ ID NO: 1)
	RHDe4A	ATCTACGTGTTCGCAGCCT (SEQ ID NO: 2)
RHD Exon 9	RHDe9S	CCAAACCTTTTAACATTAAATTATGC (SEQ ID NO: 3)
	RHDe9A	TTGGTCATCAAAATATTTAGCCTC (SEQ ID NO: 4)
RHCE Exon 2	RHCEe2S	TGTGCAGTGGGCAATCCT (SEQ ID NO: 5)
	RHCEe2A	CCACCATCCCAATACCTG (SEQ ID NO: 6)
RHCE Exon 5	RHCEe5S	AACCACCCTCTCTGGCCC (SEQ ID NO: 7)
	RHCEe5A	ATAGTAGGTGTTGAACATGGCAT (SEQ ID NO: 8)
GYPB Exon 4	GYPBe4S	ACATGTCTTTCTTATTTGGACTTAC (SEQ ID NO: 9)
	GYPBe4A	TTTGTCAAATATTAACATACCTGGTAC (SEQ ID NO: 10)
KEL Exon 6	KELe6S	TCTCTCTCCTTTAAAGCTTGGA (SEQ ID NO: 11)
	KELe6A	AGAGGCAGGATGAGGTCC (SEQ ID NO: 12)
KEL Exon 8	KELe8S	AGCAAGGTGCAAGAACACT (SEQ ID NO: 13)
	KELe8A	AGAGCTTGCCCTGTGCCC (SEQ ID NO: 14)
FY Promoter	FYproS	TGTCCCTGCCCAGAACCT (SEQ ID NO: 15)
	FYproA	AGACAGAAGGGCTGGGAC (SEQ ID NO: 16)
FY Exon 2	FYe2S	AGTGCAGAGTCATCCAGCA (SEQ ID NO: 17)

	FYe2A	TTCGAAGATGTATGGAATTCTTC (SEQ ID NO: 18)
JK Exon 9	JKe9S	CATGAACATTCCTCCCATTG (SEQ ID NO: 19)
	JKe9A	TTTAGTCCTGAGTTCTGACCCC (SEQ ID NO: 20)
DI Exon 18	DIe19S	ATCCAGATCATCTGCCTGG (SEQ ID NO: 21)
	DIe19A	CGGCACAGTGAGGATGAG (SEQ ID NO: 22)
GP3A	GP3Ae3S	ATTCTGGGGCACAGTTATCC (SEQ ID NO: 23)
	GP3Ae3A	ATAGTTCTGATTGCTGGACTTCTC (SEQ ID NO: 24)

The above primer pairs comprise the corresponding forward and reverse primers, and may be referred to herein as SEQ ID NOs 1-24.

Multiplexed single nucleotide primer extension is performed using the following 5′ tagged extension primers:

RHD Exon 4 **GTGATTCTGTACGTGTCGCCGTCTGATCTTTATCCTCCGTTCCCT** (SEQ ID NO: 25)

RHD Exon 9 **GCGGTAGGTTCCCGACATATT**TTAAACAGGTTTGCTCCTAAATCT (SEQ ID NO: 26)

RHCE Exon 2 **GGATGGCGTTCCGTCCTATT**GGACGGCTTCCTGAGCCAGTTCCCT (SEQ ID NO: 27)

RHCE Exon 5 **CGACTGTAGGTGCGTAACTC**GATGTTCTGGCCAAGTGTCAACTCT (SEQ ID NO: 28)

GYPB Exon 4 **AGGGTCTCTACGCTGACGAT***TTGAAATTTTGCTTTATAGGAGAAA* (SEQ ID NO: 29)

KEL Exon 6 **AGCGATCTGCGAGACCGTAT**TGGACTTCCTTAAACTTTAACCGAA (SEQ ID NO: 30)

KEL Exon 8 **AGATAGAGTCGATGCCAGCT**TTCCTTGTCAATCTCCATCACTTCA (SEQ ID NO: 31)

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FY Promoter **GACCTGGGTGTCGATACCTA**GGCCCTCATTAGTCCTTGGCTCTTA
(SEQ ID NO: 32)

FY Exon 2 **ACGCACGTCCACGGTGATTT**GGGGGCAGCTGCTTCCAGGTTGGCA
(SEQ ID NO: 33)

JK Exon 9 **CGTGCCGCTCGTGATAGAAT**AAACCCCAGAGTCCAAAGTAGATGT
(SEQ ID NO: 34)

DI Exon 19 **GGCTATGATTCGCAATGCTT**GTGCTGTGGGTGGTGAAGTCCACGC
(SEQ ID NO: 35)

GP3A Exon 3 **AGAGCGAGTGACGCATAC**TTGGGCTCCTGTCTTACAXGCCCTGCCTC
(SEQ ID NO: 36)

The above probes may be referred to herein as SEQ ID NOs 25-36. The DNA bases are represented by their single letter equivalents (A,C,G or T) and the letter X represents a C3 (phosphoramidite) spacer between the two adjacent DNA bases.

In this embodiment, the 12 bolded nucleotides in the 5′ region of the extension probes are hybridized to a complementary DNA sequence that has been micro-arrayed onto

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sites. The PCR primers pairs in Table 1 represent sequences complementary to DNA regions containing SNPs of interest; of which the exact sequences of each primer pair and mixture of primer pairs have been specifically optimized to amplify genomic DNA of interest as a mixture of 12 primer pairs. Although noted above, Table 2 further summarizes 12 novel extension primers specifically used together to detect the nucleotides of blood group and platelet antigen or HPA SNPs, simultaneously. The extension primers represent a group of 12 novel nucleotide sequences, of which each are a combination of: 1) a unique 5′ region necessary to direct hybridization to a micro-arrayed tag located in a specific spot in each microplate well, and 2) a 3′ region complementary to and adjacent to a SNP of a PCR-amplified DNA region containing the SNP of interest.

Table 1. The PCR primers used in the 12-pair multiplex PCR format for multiple SNP detection.

Antigen	SNP	Primer Name	Sequence 5′-3′	Product Target	Size (bp)
RhD/RhCE	C/T	RHDe4S	AGACAAACTGGGTATCGTTGC	RHD Exon 4	111
		RHDe4A	ATCTACGTGTTCGCAGCCT		
RhD/RhCE	A/G	RHDe9S	CCAAACCTTTTAACATTAAATTATGC	RHD Exon 9	98
		RHDe9A	TTGGTCATCAAAATATTTAGCCTC		
RhC/Rhc	T/C	RHCEe2S	TGTGCAGTGGGCAATCCT	RHCE Exon 2	90
		RHCEe2A	CCACCATCCCAATACCTG		
RhE/Rhe	C/G	RHCEe5S	AACCACCCTCTCTGGCCC	RHCE Exon 5	107
		RHCEe5A	ATAGTAGGTGTTGAACATGGCAT		
GYPBS/GYPBs	T/C	GYPBe4S	ACATGTCTTTCTTATTTGGACTTAC	GPYB Exon 4	103
		GYPBe4A	TTTGTCAAATATTAACATACCTGGTAC		
K/k	T/C	KELe6S	TCTCTCTCCTTTAAAGCTTGGA	KEL Exon 6	142
		KELe6A	AGAGGCAGGATGAGGTCC		
Kp^a/Kp^b	T/C	KELe8S	AGCAAGGTGCAAGAACACT	KEL Exon 8	100
		KELe8A	AGAGCTTGCCCTGTGCCC		
Fy/Fy0	T/C	FYproS	TGTCCCTGCCCAGAACCT	Duffy Promoter	90
		FYproA	AGACAGAAGGGCTGGGAC		
Fy^a/Fy^b	G/A	FYe2S	AGTGCAGAGTCATCCAGCA	Duffy Exon 2	122
		FYe2A	TTCGAAGATGTATGGAATTCTTC		
Jk^a/Jk^b	G/A	JKe9S	CATGAACATTCCTCCCATTG	Kidd Exon 9	130
		JKe9A	TTTAGTCCTGAGTTCTGACCCC		
Di^a/Di^b	T/C	DIe19S	ATCCAGATCATCTGCCTGG	Diego	90

		Die19A	CGGCACAGTGAGGATGAG	Exon 19	
HPA-1a/b	T/C	GP3Ae3S	ATTCTGGGGCACAGTTATCC	GP3A Exon 3	114
		GP3Ae3A	ATAGTTCTGATTGCTGGACTTCTC		

The above primers correspond to SEQ ID NOs 1-24, respectively, as outlined herein above.

Table 1A. Additional Blood Group and Platelet Antigen SNPs for Clinically Relevant Antigens.

Antigen	SNP			Product Target	Size (bp)
A/O GalNAc/Del	G/T			ABO Exon 6	
A/B (GalNAc/Gal)	C/G			ABO Exon 7	
A/B (GalNAc/Gal)	G/A			ABO Exon 7	
A/B (GalNAc/Gal)	C/A			ABO Exon 7	
A/B (GalNAc/Gal)	G/C			ABO Exon 7	
M/N	G/A			MNS Exon 2	
M/N	T/G			MNS Exon 2	
MNS/MiI	C/T			MNS Exon 3	
RHD/Weak D Type 1	T/G			RHD Exon 6	
RHD/Weak D Type 2	G/C			RHD Exon 9	
RHD/Weak D Type 3	C/G			RHD Exon 1	
RHD/D nt602 Variants	C/G			RHD Exon 4	
RHD/'DAR' Variant	T/C			RHD Exon 7	
RHD/Weak D Type 5	C/A			RHD Exon 3	
RHD/D_{el}	G/A			RHD IVS3+1	
RHD/D_{el}	G/T			RHD Exon 6	
RHD/D_{el}	G/A			RHD Exon 9	
RHD/RHDψ nt506	A/T			RHD Exon 4	
RHCE/RhC	T/C			RHCE IVS2+1722	

Each antigen listed on the left represents a blood group or HPA genotype and the single nucleotide polymorphism (SNP). Some genotypes are evaluated using more than one SNP because they differ by more than one nucleotide. Each PCR primer pair consists of a sense (Primer Name ending in S) and antisense (Primer Name ending in A) oligonucleotide (Sequence 5'-3') designed to amplify the DNA region containing the SNP for the antigen of interest. The target region (Product Target) and the amplified fragment (Size (bp)) are shown on the right. Note that 12 SNPs are evaluated for 19 different blood group and platelet antigens because some antigens have more than one SNP. In some cases an A or G SNP is included since the complementary DNA strand can be evaluated as it will contain the T or C SNP of interest.

Table 2. Extension probes used to detect the nucleotides of blood group and HPA SNPs.

Name	Sequence 5'-3'
RHD Exon 4	GTGATTCTGTACGTGTCGCCGTCTGATCTTTATCCTCCGTTCCCT
RHD Exon 9	GCGGTAGGTTCCCGACATATTTTAAACAGGTTTGCTCCTAAATCT
RHCE Exon 2	GGATGGCGTTCCGTCCTATTGGACGGCTTCCTGAGCCAGTTCCCT
RHCE Exon 5	CGACTGTAGGTGCGTAACTCGATGTTCTGGCCAAGTGTCAACTCT
GYPB Exon 4	AGGGTCTCTACGCTGACGATTTGAAATTTTGCTTTATAGGAGAAA
KEL Exon 6	AGCGATCTGCGAGACCGTATTGGACTTCCTTAAACTTTAACCGAA
KEL Exon 8	AGATAGAGTCGATGCCAGCTTTCCTTGTCAATCTCCATCACTTCA
FY Promoter	GACCTGGGTGTCGATACCTAGGCCCTCATTAGTCCTTGGCTCTTA
FY Exon 2	ACGCACGTCCACGGTGATTTGGGGGCAGCTGCTTCCAGGTTGGCA
JK Exon 9	CGTGCCGCTCGTGATAGAATAAACCCCAGAGTCCAAAGTAGATGT
Di Exon 19	GGCTATGATTCGCAATGCTTGTGCTGTGGGTGGTGAAGTCCACGC
GP3A Exon 3	AGAGCGAGTGACGCATACTTGGGCTCCTGTCTTACAXGCCCTGCCTC

The above probes correspond to SEQ ID NOs 25-36, respectively, as identified herein above. The DNA bases are represented by their single letter equivalents (A,C,G or T) and the letter X represents a C3 (phosphoramidite) spacer between the two adjacent DNA bases.

The present invention also provides novel hybrid probes, wherein the preferred probes are listed in Table 2, but limited to said listing. Each extension probe is

automatically generated using the SNPStream Software Suite of MegaImage, UHTGetGenos and QCReview.

It should be noted that the specific steps associated with the protocol exemplified in Example 1 are not intended to limit the teachings and methods of the present invention to the specific above protocol. Example 1 is provided to specify a preferred method in accordance with the present invention wherein a plurality of blood group and HPA SNPs are simultaneously analysed in a ultra high throughput multiplex automated system for the determination of the specific genotypes and accordingly the phenotypes associated therewith. Accordingly, it should be understood by one skilled in the art that the steps of Example 1 may be varied provided that such variations yield the preferred results of the present invention.

RESULTS

1. GP3A Exon 3 SNP Scatter Plots.

The robotic UHT platform produces laser-fluorescence values for each sample which are represented in 'scatter plots' for the operator to review. A sample scatter plot is shown in Fig. 1 for the SNP analysis GP3A Exon 3, which represents the HPA-1a and HPA-1b antigens. As can been seen in Fig. 1 and Fig. 4, results are graphed using logarithmic and XY scatter plots (upper right). Green O, orange □ or blue O sample designations represent CC, TC and TT SNP genotype calls, respectively, with corresponding graphical summaries appearing in the respective legends of each figure. No fluorescence represents an assay failure (FL) for that sample.

Scatter plots (as shown in Fig. 1 and Fig. 4) are generated preferably using SNPStream software suite and viewed through QCReview. It should be additionally noted that the present analysis is not limited to SNPstream or

Appendix A

Genotype Results for updated 12 SNP CBS Panel

SampleID	rs[illegible]	rs[illegible]	rs[illegible]	rs[illegible]	rs[illegible]
BB24401	FL	FL	FL	FL	FL
BB24402	TT	FL	CC	CC	TC
BB24407	TC	TT	TC	TC	TC
BB24408	TC	TT	TC	TC	CC
BB24409	TC	TT	TC	TC	TC
BB24410	TC	TT	TC	TC	TC
BB24415	TC	TT	TC	TC	FL
BB24416	FL	FL	FL	FL	FL
BB24417	TC	TT	TC	FL	TC
BB24420	TC	TT	TC	TC	CC
BB24421	TC	TT	TC	TC	CC
BB24422	TC	TT	TC	FL	TC
BB24423	TC	TT	TC	TC	TC
BB24424	TC	TT	TC	FL	TC
BB24425	TC	TT	TC	TC	CC
BB24426	TC	TT	TC	TC	TC
BB24427	TC	TT	TC	TC	TC
BB24428	TC	TT	TC	TC	CC
BB24429	TC	TT	TC	TC	CC
BB24430	TC	TT	TC	TC	TC
BB24431	TC	TT	TC	TC	CC
BB24432	TC	TT	TC	TC	CC
BB24433	TC	TT	TC	TC	CC
BB24434	TC	TT	TC	TC	CC
BB24435	TC	TT	TC	TC	CC
BB24436	TT	FL	CC	CC	TC
BB24437	TC	TT	TC	TC	TC
BB24438	TC	TT	TC	TC	TC
BB24439	TC	TT	TC	TC	CC
BB24440	TC	TT	TC	FL	TC
BB24444	TC	TT	TC	TC	CC
BB24448	TT	FL	CC	CC	FL
BB24461	TC	TT	TC	TC	CC
BB24462	TT	FL	CC	CC	TC
BB24463	TC	TT	TC	TC	CC
BB24464	TC	TT	TC	TC	CC
BB24465	TC	TT	TC	TC	TC
BB24466	TC	TT	TC	FL	TC
BB24467	TT	FL	CC	CC	TC
BB24468	TC	TT	TC	FL	TC
BB24469	TC	TT	TC	TC	CC
BB24470	TT	FL	CC	CC	TC
BB24471	TC	TT	TC	TC	TC
BB24472	TC	TT	TC	TC	TC
BB24473	TC	TT	TC	TC	TC
BB24474	TC	TT	TC	TC	TC
BB24475	TC	TT	TC	TC	TC
BB24476	TC	TT	TC	TC	CC
BB24477.	TC	TT	TC	TC	TC
BB24478	TC	TT	TC	TC	TC
BB24479	TC	TT	TC	TC	TC
BB24480	TC	TT	TC	TC	TC

BB24481	TC	TT	TC	TC	CC
BB24482	TC	TT	TC	TC	TC
BB24483	TT	FL	CC	CC	TC
BB24484	TC	TT	TC	TC	TC
BB24485	TT	FL	CC	FL	TC
BB24486	TT	FL	CC	CC	TC
BB24487	TC	TT	TC	TC	TC
BB24488	TC	TT	TC	TC	TC
BB24489	TC	TT	TC	TC	TC
BB24491	TC	TT	TC	TC	TC
BB24492	TT	FL	CC	CC	TC
BB24493	TT	FL	CC	CC	TC
BB24494	FL	FL	FL	FL	FL
BB24495	TC	TT	TC	TC	TC
BB24496	TC	TT	TC	TC	TC
BB24497	TC	TT	TC	TC	CC
BB24499	TC	TT	TC	TC	TC
BB24504	TC	TT	TC	TC	TC
BB24505	TC	TT	TC	TC	TC
BB24506	TC	TT	TC	TC	CC
BB24507	TC	TT	TC	TC	CC
BB24512	TT	FL	CC	CC	TC
BB24513	TC	TT	TC	FL	TC
BB24516	TC	TT	TC	TC	CC
BB24517	TT	FL	CC	CC	TC
BB24518	TC	TT	TC	TC	TC
BB24519	TC	TT	TC	TC	CC
BB24522	TC	TT	TC	TC	CC
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BB24526	TC	TT	TC	TC	CC
BB24527	TT	FL	CC	CC	TC
BB24528	TC	TT	TC	TC	TC
BB24529	TC	TT	TC	TC	TC
BB24530	TC	TT	TC	TC	CC
BB24531	FL	FL	FL	FL	FL
BB24532	TC	TT	TC	TC	CC
BB24533	TC	TT	TC	TC	TC
BB24534	TC	TT	TC	FL	TC
BB24535	TC	TT	TC	TC	TC
BB24536	TC	TT	TC	TC	TC
BB24537	TC	TT	TC	TC	CC
BB24538	TC	TT	TC	TC	CC
BB24539	TC	TT	TC	TC	CC
BB24540	TC	TT	TC	TC	TC
BB24541	TC	TT	TC	FL	TC
BB24542	TC	TT	TC	TC	CC
BB24543	TC	TT	TC	TC	CC
BB24547	FL	FL	FL	FL	FL
BB24548	TT	FL	CC	CC	TC
BB24549	TT	FL	CC	CC	FL
BB24550	TC	TT	TC	TC	TC
BB24552	TC	TT	TC	TC	TC
BB24553	TC	TT	TC	TC	CC
BB24554	TC	TT	TC	FL	TC

BB24555	TC	TT	TC	TC	TC
BB24556	TC	TT	TC	TC	CC
BB24557	TC	TT	TC	TC	CC
BB24558	TC	TT	TC	TC	TC
BB24559	TC	TT	TC	TC	TC
BB24560	TT	FL	CC	CC	CC
BB24561	TC	TT	TC	FL	TC
BB24562	TC	TT	TC	TC	CC
BB24563	TT	FL	CC	CC	TC
BB24564	TC	TT	TC	TC	CC
BB24565	TC	TT	TC	TC	TC
BB24566	TT	FL	CC	CC	TC
BB24567	TC	TT	TC	TC	CC
BB24568	TC	TT	TC	TC	CC
BB24569	TC	TT	TC	TC	TC
BB24570	TC	TT	TC	FL	TC
BB24571	TC	TT	TC	TC	TC
BB24572	TT	FL	CC	CC	TC
BB24573	TC	TT	TC	TC	TC
BB24574	TT	FL	CC	CC	TC
BB24575	TT	FL	CC	CC	TC
BB24576	TC	TT	TC	TC	TC
BB24577	TC	TT	TC	TC	TC
BB24578	TC	TT	TC	TC	TC
BB24579	TC	TT	TC	TC	TC
BB24580	TT	FL	FL	CC	TC
BB24581	TC	TT	TC	TC	TC
BB24586	TC	TT	TC	TC	TC
BB24587	TC	TT	TC	TC	CC
BB24594	TC	TT	TC	TC	TC
BB24600	TC	TT	TC	FL	TC
BB24601	TC	TT	TC	FL	TC
BB24602	TC	TT	TC	TC	CC
BB24603	TC	TT	TC	FL	TC
BB24604	TC	TT	TC	TC	TC
BB24605	TC	TT	TC	TC	TC
BB24606	TC	TT	TC	TC	CC
BB24607	TC	TT	TC	TC	TC
BB24608	TC	TT	TC	TC	CC
BB24609	TC	TT	TC	FL	TC
BB24610	TT	FL	CC	CC	TC
BB24611	TC	TT	TC	TC	CC
BB24612	TC	TT	TC	TC	CC
BB24613	TC	TT	TC	TC	TC
BB24614	TC	TT	TC	TC	CC
BB24615	TC	TT	TC	TC	CC
BB24616	TC	TT	TC	TC	TC
BB24617	TC	TT	TC	FL	TC
BB24618	TC	TT	TC	TC	TC
BB24619	TC	TT	TC	FL	FL
BB24620	TC	TT	TC	FL	FL
BB24621	TC	TT	TC	TC	TC
BB24622	TC	TT	TC	FL	TC
BB24623	TT	FL	CC	CC	TC
BB24624	TT	FL	CC	CC	TC
BB24625	TC	TT	TC	TC	TC

BB24626	TC	TT	TC	TC	CC
BB24627	TC	TT	TC	TC	TC
BB24628	TC	TT	TC	TC	TC
BB24629	FL	FL	FL	FL	FL
BB24630	TC	TT	TC	TC	CC
BB24631	TC	TT	TC	FL	TC
BB24632	TC	TT	TC	TC	TC
BB24633	TC	TT	TC	FL	TC
BB24634	TC	TT	TC	TC	TC
BB24635	TC	TT	TC	TC	TC
BB24636	TC	TT	TC	FL	TC
BB24637	TC	TT	TC	FL	TC
BB24638	TC	TT	TC	TC	TC
BB24639	TT	FL	CC	CC	TC
BB24640	TC	TT	TC	TC	CC
BB24641	TT	FL	CC	CC	TC
BB24642	TC	TT	TC	TC	CC
BB24643	TC	TT	TC	TC	CC
BB24644	TT	FL	FL	FL	TC
BB24645	TC	TT	TC	TC	CC
BB24646	TT	FL	CC	CC	TC
BB24647	TC	TT	TC	TC	TC
BB24648	TC	TT	TC	TC	TC
BB24649	TC	TT	TC	TC	TC
BB24650	FL	FL	FL	FL	FL
BB24651	TC	TT	TC	TC	TC
BB24652	TC	TT	TC	TC	TC
BB24653	TC	TT	TC	TC	TC
BB24654	TC	TT	TC	TC	TC
BB24655	TT	FL	CC	CC	TC
BB24656	TT	FL	CC	CC	TC
BB24657	FL	FL	FL	FL	FL
BB24658	TT	FL	CC	CC	TC
BB24659	TC	TT	TC	TC	TC
BB24660	TT	FL	CC	CC	TC
BB24661	TC	TT	TC	TC	TC
BB24662	TC	TT	TC	TC	TC
BB24663	TC	TT	TC	TC	TC
BB24664	TC	TT	TC	TC	TC
BB24665	TT	FL	FL	CC	TC
BB24666	TC	TT	TC	FL	TC
BB24667	TC	TT	TC	TC	CC
BB24668	TC	TT	TC	TC	CC
BB24669	TC	TT	TC	TC	CC
BB24670	TC	TT	TC	TC	CC
BB24672	TC	TT	TC	TC	TC
BB24673	TC	TT	TC	TC	TC
BB24674	TC	TT	TC	TC	CC
BB24675	TC	TT	TC	TC	TC
BB24676	TC	TT	TC	FL	TC
BB24678	TT	FL	CC	CC	TC
BB24679	TC	FL	TC	TC	TC
BB24680	TC	TT	TC	TC	CC
BB24681	TC	TT	TC	TC	TC
BB24682	TC	TT	TC	TC	TC
BB24683	TT	FL	CC	CC	TC

BB24684	TC	TT	TC	TC	CC
BB24685	TC	TT	TC	TC	CC
BB24686	TC	TT	TC	TC	CC
BB24687	TC	TT	TC	TC	TC
BB24688	TT	FL	CC	CC	TC
BB24689	TC	TT	TC	TC	CC
BB24690	TC	TT	TC	TC	CC
BB24691	TC	TT	TC	TC	CC
BB24692	TC	TT	TC	TC	CC
BB24693	TC	TT	TC	TC	TC
BB24694	TT	FL	CC	CC	TC
BB24695	TT	FL	CC	CC	TC
BB24696	TC	TT	TC	TC	CC
BB24697	TC	TT	TC	TC	TC
BB24698	TC	TT	TC	TC	CC
BB24699	TC	TT	TC	TC	TC
BB24700	FL	FL	FL	FL	FL
BB24701	TT	FL	CC	CC	TC
BB24702	TT	FL	CC	CC	TC
BB24703	TT	FL	CC	CC	TC
BB24704	TC	TT	TC	FL	TC
BB24705	TC	TT	TC	TC	TC
BB24706	TT	FL	FL	CC	TC
BB24707	TC	TT	TC	TC	CC
BB24708	TC	TT	TC	FL	TC
BB24709	TC	TT	TC	TC	TC
BB24710	TC	TT	TC	TC	CC
BB24711	TC	FL	TC	TC	TC
BB24712	TC	TT	TC	TC	TC
BB24713	TC	FL	TC	FL	TC
BB24714	TT	FL	CC	CC	TC
BB24715	TT	FL	CC	CC	TC
BB24716	TC	TT	TC	TC	CC
BB24717	TC	TT	TC	TC	TC
BB24718	TC	TT	TC	TC	TC
BB24719	TC	TT	TC	TC	TC
BB24720	TC	TT	TC	TC	CC
BB24721	TC	TT	TC	TC	TC
BB24722	TC	TT	TC	TC	TC
BB24723	TC	TT	TC	TC	CC
BB24724	TC	TT	TC	TC	TC
BB24725	TT	FL	CC	CC	TC
BB24726	TC	TT	TC	TC	TC
BB24727	TC	TT	TC	TC	CC
BB24728	TC	TT	TC	TC	TC
BB24729	TC	TT	TC	FL	TC
BB24730	TC	FL	TC	TC	CC
BB24731	TC	TT	TC	TC	CC
BB24732	TT	FL	CC	CC	TC
BB24733	TC	TT	TC	TC	TC
BB24734	TC	TT	TC	TC	CC
BB24735	TT	FL	CC	CC	TC
BB24736	TC	TT	TC	TC	TC
BB24737	TC	TT	TC	FL	TC
BB24738	TT	FL	CC	CC	TC
BB24739	TT	FL	CC	CC	TC

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BB24740	FL	FL	FL	FL	FL
BB24741	TC	TT	TC	TC	TC
BB24742	TC	TT	TC	TC	TC
BB24743	TC	TT	TC	TC	TC
BB24744	TC	TT	TC	TC	TC
BB24745	TC	TT	TC	TC	TC
BB24746	TC	TT	TC	TC	TC
BB24747	TC	TT	TC	TC	CC
BB24748	TC	TT	TC	TC	TC
BB24749	TT	FL	CC	CC	CC
BB24750	TC	TT	TC	TC	TC
BB24751	TC	TT	TC	TC	TC
BB24752	TC	TT	TC	TC	TC
BB24753	FL	FL	FL	FL	FL
BB24754	TC	TT	TC	TC	CC
BB24755	TT	FL	CC	CC	TC
BB24756	TC	FL	TC	TC	CC
BB24757	TC	TT	TC	FL	TC
BB24758	TC	TT	TC	TC	TC
BB24759	TC	TT	TC	TC	TC
BB24760	TC	TT	TC	TC	TC
BB24761	TC	TT	TC	TC	CC
BB24762	TC	TT	TC	TC	TC
BB24763	TC	TT	TC	TC	FL
BB24764	TT	FL	CC	TC	TC
BB24765	TC	FL	TC	TC	CC
BB24766	TC	TT	TC	FL	TC
BB24767	TC	TT	TC	TC	TC
BB24768	TC	TT	TC	FL	TC
BB24769	TC	TT	TC	TC	CC
BB24770	TT	FL	CC	CC	CC
BB24771	TC	TT	TC	TC	TC
BB24772	TC	TT	TC	TC	TC
BB24773	TC	TT	TC	TC	TC
BB24774	TC	TT	TC	TC	CC
BB24775	TC	TT	TC	TC	TC
BB24776	TC	TT	TC	TC	TC
BB24777	TC	TT	TC	TC	TC
BB24778	TC	TT	TC	TC	CC
BB24779	TC	FL	TC	TC	CC
BB24780	TC	TT	TC	TC	TC
BB24781	TC	TT	TC	TC	TC
BB24782	TC	TT	TC	TC	TC
BB24783	TT	FL	CC	CC	TC
BB24784	TC	TT	TC	TC	TC
BB24785	TC	TT	TC	TC	TC
BB24786	TC	TT	TC	TC	TC
BB24787	TC	TT	TC	TC	TC
BB24788	TC	TT	TC	TC	CC
BB24789	TC	TT	TC	TC	TC
BB24790	TT	FL	CC	CC	TC
BB24791	TT	FL	CC	FL	TC
BB24792	TC	TT	TC	TC	CC
BB24793	TT	FL	CC	CC	FL
BB24794	TC	TT	TC	TC	CC
BB24795	TC	TT	TC	TC	TC

BB24796	TC	TT	TC	TC	TC
BB24797	TC	TT	TC	TC	TC
BB24798	TC	TT	TC	TC	TC
BB24799	TC	TT	TC	TC	TC
BB24800	TC	TT	TC	TC	TC
BB24801	FL	FL	FL	FL	FL
BB24803	TC	TT	TC	TC	CC
BB24804	TT	FL	CC	CC	TC
BB24805	TC	TT	TC	TC	CC
BB24806	TC	TT	TC	TC	CC
BB24807	TC	TT	TC	FL	TC
BB24808	TC	TT	TC	TC	TC
BB24809	TC	TT	TC	TC	TC
BB24810	TC	TT	TC	TC	CC
BB24811	FL	FL	FL	FL	FL
BB24812	TC	TT	TC	TC	TC
BB24815	TC	TT	TC	TC	TC
BB24817	TC	TT	TC	TC	TC
BB24818	TC	TT	TC	TC	TC
BB24819	TC	TT	TC	TC	CC
BB24820	TC	TT	TC	TC	TC
BB24821	TT	FL	CC	CC	TC
BB24823	TC	TT	TC	TC	TC
BB24824	TC	TT	TC	TC	TC
BB24826	TC	TT	TC	TC	TC
BB24827	TT	FL	CC	TC	TC
BB24830	TC	TT	TC	TC	TC
BB24831	TC	TT	TC	TC	CC
BB24832	TT	FL	CC	CC	TC
BB24833	TC	TT	TC	TC	TC
BB24834	TC	TT	TC	TC	CC
BB24836	TC	TT	TC	TC	TC
BB24837	TC	TT	TC	TC	TC
BB24838	TC	TT	TC	TC	TC
BB24839	TC	TT	TC	TC	CC
BB24841	TC	TT	TC	TC	TC
BB24842	TC	TT	TC	TC	TC
BB24843	TT	FL	FL	TC	FL
BB24844	FL	FL	FL	FL	FL
BB24847	TC	TT	TC	TC	CC
Q1H2O	FL	FL	FL	FL	FL
Q2H2O	FL	FL	FL	FL	FL
Q3H2O	FL	FL	FL	FL	FL
Q4H2O	FL	FL	FL	FL	FL

	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Sample FL	15	86	20	54	23
Sample Pass	357	286	352	318	349
Call Rate	95.97%	76.88%	94.62%	85.48%	93.82%
Genotypes (N)					
XX (TT)	64	286	0	0	0
XY (TC)	293	0	293	260	246
YY (CC)	0	0	59	58	103
Allele Freq					
X (p)	58.96%	100.00%	41.62%	40.88%	35.24%
Y (q)	41.04%	0.00%	58.38%	59.12%	64.76%

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FL	FL	FL	FL	FL	FL
CC	CC	CC	TT	CC	TC
CC	CC	CC	TT	TT	TC
CC	CC	CC	TT	CC	TT
CC	CC	CC	TT	CC	CC
CC	CC	CC	TT	TC	TT
CC	CC	CC	TT	TT	TT
FL	FL	FL	FL	FL	FL
CC	CC	CC	TT	CC	TT
CC	CC	CC	TT	CC	TT
CC	CC	CC	TT	TC	TT
CC	CC	CC	TT	TC	TC
TC	CC	CC	TT	TC	TT
CC	CC	CC	TT	CC	TT
CC	CC	CC	TT	TT	TT
TC	CC	CC	TT	TC	TC
CC	CC	CC	TT	TT	TT
CC	CC	CC	TT	TC	TT
TC	CC	CC	TT	TT	TC
TC	CC	CC	TT	TT	TC
CC	CC	CC	TT	TT	TC
CC	CC	CC	TT	TC	TT
CC	CC	CC	TT	CC	TT
CC	CC	CC	TT	TC	TT
CC	CC	CC	TT	TC	TT
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CC	CC	CC	TT	TT	TT
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CC	CC	CC	TT	TC	TT
CC	CC	CC	TT	TC	TC
CC	CC	CC	TT	TC	TT
CC	CC	CC	TT	TT	TT
CC	CC	CC	TT	TC	TC
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CC	CC	CC	TT	CC	TT
CC	CC	CC	TT	TC	TT
CC	CC	CC	TT	TT	CC
CC	CC	CC	TT	TT	TT
TC	CC	CC	TT	TC	TC
TC	CC	CC	TT	TT	TT
CC	CC	CC	TT	CC	TT
CC	CC	CC	TT	TC	TT
CC	CC	CC	TT	TT	TT
CC	CC	CC	TT	CC	TT
CC	CC	CC	TT	TT	TT
CC	CC	CC	TT	TT	TT
CC	CC	CC	TT	TC	TT

AMENDED SHEET

CC	CC	CC	TT	CC	TT
CC	CC	CC	TT	TC	TT
CC	CC	CC	TT	TT	TT
TC	CC	CC	TT	CC	TC
TC	CC	CC	TT	TC	TC
CC	CC	CC	TT	TT	TT
CC	CC	CC	TT	TT	TC
CC	CC	CC	TT	CC	TT
CC	CC	CC	TT	TT	TC
CC	CC	CC	TT	TT	TT
CC	CC	CC	TT	CC	TT
CC	CC	CC	TT	TC	TT
FL	FL	FL	FL	FL	FL
CC	CC	CC	TT	TC	TC
CC	CC	CC	TT	TT	TT
CC	CC	CC	TT	TC	TC
CC	CC	CC	TT	TT	TT
CC	CC	CC	TT	TT	TC
CC	CC	CC	TT	CC	TC
CC	CC	CC	TT	TC	TC
CC	CC	CC	TT	TC	TT
FL	FL	FL	FL	FL	FL
CC	CC	CC	TT	CC	TT
CC	CC	CC	TT	TC	TT
CC	CC	CC	TT	TC	TT
CC	CC	CC	TT	CC	TT
CC	CC	CC	TT	CC	TT
CC	CC	CC	TT	TC	TT
CC	CC	CC	TT	TC	TC
FL	FL	FL	FL	FL	FL
CC	CC	CC	TT	TT	TT
CC	CC	CC	TT	CC	TT
TC	CC	CC	TT	TT	TT
TC	CC	CC	TT	TC	TT
CC	CC	CC	TT	TC	TT
CC	CC	CC	TT	TT	TT
CC	CC	CC	TT	TT	TT
CC	CC	CC	TT	TC	TT
CC	CC	CC	TT	TC	TT
CC	CC	CC	TT	TT	TT
CC	CC	CC	TT	TC	TT
CC	CC	CC	TT	CC	TT
FL	FL	FL	FL	FL	FL
CC	CC	CC	TT	CC	TT
CC	CC	CC	TT	TC	TT
CC	CC	CC	TT	TC	TT
CC	CC	CC	TT	TC	TT
CC	CC	CC	TT	CC	TT
CC	CC	CC	TT	TT	TT

AMENDED SHEET

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CC	CC	CC	TT	TC	TC
CC	CC	CC	TT	CC	TT
TC	CC	CC	TT	TC	TC
FL	FL	FL	FL	FL	FL
CC	CC	CC	TT	TT	TT
CC	CC	CC	TT	CC	TT
CC	CC	CC	TC	TT	TT
CC	CC	CC	TT	TT	TC
CC	CC	CC	TT	CC	TT
CC	CC	CC	TT	CC	TT
CC	CC	CC	TT	CC	TT
CC	CC	CC	TT	TT	TT
CC	CC	CC	TT	CC	TT
CC	CC	CC	TT	CC	TT
CC	CC	CC	TT	TT	TT
CC	CC	CC	TT	TT	TT
CC	CC	CC	TT	TC	TT
CC	CC	CC	TT	TC	TT
FL	CC	CC	TT	TC	TT
CC	CC	CC	TT	TT	TT
CC	CC	CC	TT	TT	TT
TC	CC	CC	TT	TC	TT
CC	CC	CC	TT	CC	TT
CC	CC	CC	TT	TT	TC
FL	FL	FL	FL	FL	FL
CC	CC	CC	TT	TC	TT
CC	CC	CC	TT	TC	TT
CC	CC	CC	TT	CC	TC
CC	CC	CC	TT	CC	TT
CC	CC	CC	TT	TC	TC
CC	CC	CC	TT	TT	TC
FL	FL	FL	FL	FL	FL
CC	CC	CC	TT	CC	TT
CC	CC	CC	TT	TC	TC
CC	CC	CC	TT	TT	TT
CC	CC	CC	TT	TC	TT
CC	CC	CC	TT	TC	TC
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FL	CC	FL	TT	TC	CC
CC	CC	CC	TT	TT	TT
CC	CC	CC	TT	TC	TC
CC	CC	CC	TT	TT	TT
TC	CC	CC	TT	CC	TC
CC	CC	CC	TT	TC	TT
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CC	CC	CC	TT	TC	TT
CC	CC	CC	TT	CC	TT
CC	CC	CC	TT	TT	TT
CC	CC	CC	TT	TC	TT
CC	CC	CC	TT	CC	TT
CC	CC	CC	TT	TC	TC

CC	CC	CC	TT	TC	TC
CC	CC	CC	CC	TT	TT
CC	CC	CC	TT	CC	TC
CC	CC	CC	TT	CC	TC
CC	CC	CC	TT	TC	TT
CC	CC	CC	TT	TC	TT
CC	CC	CC	TT	CC	TC
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CC	CC	CC	TT	TC	TT
CC	CC	CC	TT	CC	TT
CC	CC	CC	TT	TC	TT
CC	CC	CC	TT	TT	TT
CC	CC	CC	TT	TT	TT
TC	CC	CC	TT	TT	TT
CC	CC	CC	TT	TT	TT
CC	CC	CC	TT	TC	TT
FL	FL	FL	FL	FL	FL
CC	CC	CC	TT	TT	TT
CC	CC	CC	TT	TC	TC
CC	CC	CC	TT	TC	TT
CC	CC	CC	TT	CC	TT
CC	CC	CC	TT	TC	TT
CC	CC	CC	TT	CC	TT
CC	CC	CC	TT	TC	TT
CC	CC	CC	TT	TC	TC
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CC	CC	CC	TT	TC	TT
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CC	CC	CC	TT	CC	TT
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CC	CC	CC	TT	TT	TC
CC	CC	CC	TT	TT	TC
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CC	CC	CC	TT	TT	TC
CC	CC	CC	TT	TT	TC
CC	CC	CC	TT	TT	TT
CC	CC	CC	TT	TC	TT
TC	CC	CC	TT	TC	TT
CC	CC	CC	TT	TT	TT
TC	CC	CC	TT	TC	TT
CC	CC	CC	TT	TT	TT
CC	CC	CC	TT	TC	TC
CC	CC	CC	TT	TC	TC

AMENDED SHEET

FL	FL	FL	FL	FL	FL
CC	CC	CC	TT	TC	TT
CC	CC	CC	TC	TT	TT
CC	CC	CC	TT	TT	TT
CC	CC	CC	TT	TT	TC
CC	CC	CC	TT	CC	TT
CC	CC	CC	TT	TC	TT
CC	CC	CC	TT	TC	TT
CC	CC	CC	TT	TC	TT
CC	CC	CC	TT	TC	TT
CC	CC	CC	TT	TC	TT
CC	CC	CC	TC	TC	TT
CC	CC	CC	TT	TT	TC
FL	FL	FL	FL	FL	FL
CC	CC	CC	TT	TC	TC
CC	CC	CC	TT	TC	TT
CC	CC	CC	TT	TT	TC
CC	CC	CC	TT	TT	TT
CC	CC	CC	TT	CC	TC
CC	CC	CC	TT	CC	TT
CC	CC	CC	TT	TC	TC
CC	CC	CC	TT	TC	TT
CC	CC	CC	TT	TC	TT
TC	CC	CC	TT	CC	FL
CC	TC	CC	TT	TT	TT
CC	CC	CC	TT	TT	TT
CC	CC	CC	TT	TC	TT
CC	CC	CC	TT	CC	TT
CC	CC	CC	TT	TT	TT
CC	CC	CC	TT	CC	TT
CC	CC	CC	TT	CC	TT
CC	CC	CC	TT	TC	TT
CC	CC	CC	TT	TC	TT
CC	CC	CC	TT	TT	TC
CC	CC	CC	TT	CC	TT
CC	CC	CC	TT	CC	TT
CC	CC	CC	TT	TT	TT
CC	CC	CC	TT	TC	TT
CC	FL	CC	TT	TT	TT
CC	CC	CC	TT	TC	TC
CC	CC	CC	TT	TC	TC
CC	CC	CC	TT	CC	TT
CC	CC	CC	TT	TC	TC
CC	CC	CC	TT	CC	TT
CC	CC	CC	TT	TC	TT
CC	CC	CC	TT	TT	TT
TC	CC	CC	TT	TT	TC
CC	CC	CC	TT	TT	TC
TC	CC	CC	TT	TT	TT
CC	CC	CC	TC	TT	TT
CC	FL	CC	TT	TC	TT
TC	CC	CC	TT	TT	TT
CC	CC	CC	TT	TT	TT
CC	CC	CC	TT	CC	TC
CC	CC	CC	TT	CC	TT

AMENDED SHEET

CC	CC	CC	TT	TC	TT
CC	CC	TC	TT	TT	TT
CC	CC	CC	TT	CC	TT
CC	CC	CC	TT	TC	TT
CC	CC	CC	TT	TC	TT
FL	FL	FL	FL	FL	FL
CC	CC	CC	TT	CC	TT
CC	CC	CC	TT	TC	TT
CC	CC	CC	TT	TT	TT
CC	CC	CC	TT	TC	TT
CC	CC	CC	TC	TT	TT
CC	CC	CC	TT	TC	TT
CC	CC	CC	TT	TC	TC
CC	CC	CC	TT	TC	TT
FL	FL	FL	FL	FL	FL
CC	CC	CC	TT	TC	TT
CC	CC	CC	TT	TT	TC
CC	CC	CC	TT	CC	TT
CC	CC	CC	TT	TC	TT
CC	CC	CC	TT	CC	TT
CC	CC	CC	TT	CC	TT
CC	CC	CC	TT	CC	TT
CC	CC	CC	TT	CC	TT
CC	CC	CC	TT	TT	TT
CC	CC	CC	TT	TC	TC
CC	CC	CC	TT	TC	TT
CC	CC	CC	TT	TT	TT
CC	CC	CC	TT	TC	TT
CC	CC	CC	TT	CC	TT
TC	CC	CC	TT	TC	TT
CC	CC	CC	TT	TT	TT
CC	CC	CC	TT	TC	TC
FL	CC	FL	TT	FL	TC
FL	FL	FL	FL	FL	FL
TC	CC	CC	TT	TT	TT
FL	FL	FL	FL	FL	FL
FL	FL	FL	FL	FL	FL
FL	FL	FL	FL	FL	FL
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
18	17	17	15	16	16
354	355	355	357	356	356
95.16%	95.43%	95.43%	95.97%	95.70%	95.70%
0	0	0	348	112	263
28	1	2	7	155	89
326	354	353	2	89	4
3.95%	0.14%	0.28%	98.46%	53.23%	86.38%
96.05%	99.86%	99.72%	1.54%	46.77%	13.62%

AMENDED SHEET

IR6	Sample FL	Pass Rate
FL	12	0.0%
CC	1	91.7%
TC	0	100.0%
TC	0	100.0%
TC	0	100.0%
TC	0	100.0%
TC	1	91.7%
FL	12	0.0%
TC	1	91.7%
CC	0	100.0%
TT	0	100.0%
TC	1	91.7%
TT	0	100.0%
TC	1	91.7%
TC	0	100.0%
TC	0	100.0%
CC	0	100.0%
TC	0	100.0%
TC	0	100.0%
CC	0	100.0%
TT	0	100.0%
TT	0	100.0%
TC	0	100.0%
TT	0	100.0%
TC	0	100.0%
TC	1	91.7%
TT	0	100.0%
TT	0	100.0%
TC	0	100.0%
TC	1	91.7%
TC	0	100.0%
CC	2	83.3%
CC	0	100.0%
CC	1	91.7%
TC	0	100.0%
TC	0	100.0%
TC	0	100.0%
TC	1	91.7%
TC	1	91.7%
TC	1	91.7%
TC	0	100.0%
CC	1	91.7%
TC	0	100.0%
CC	0	100.0%
CC	0	100.0%
TT	0	100.0%
TC	0	100.0%
TC	0	100.0%
TC	0	100.0%
TC	0	100.0%
TC	0	100.0%
TC	0	100.0%
CC	0	100.0%

AMENDED SHEET

TT		0	100.0%
TC		0	100.0%
TC		1	91.7%
TC		0	100.0%
TC		2	83.3%
TT		1	91.7%
CC		0	100.0%
TC		0	100.0%
CC		0	100.0%
TC		0	100.0%
CC		1	91.7%
TC		1	91.7%
FL		12	0.0%
TC		0	100.0%
CC		0	100.0%
TC		0	100.0%
CC		0	100.0%
TC		0	100.0%
TC		0	100.0%
TC		0	100.0%
TC		0	100.0%
TC		1	91.7%
CC		0	100.0%
TT		0	100.0%
FL		12	0.0%
TC		0	100.0%
TT		1	91.7%
TC		0	100.0%
TC		1	91.7%
TC		0	100.0%
TC		0	100.0%
CC		0	100.0%
FL		12	0.0%
TC		0	100.0%
CC		0	100.0%
TT		1	91.7%
TC		0	100.0%
TT		0	100.0%
TC		0	100.0%
TT		0	100.0%
TC		0	100.0%
TC		1	91.7%
CC		0	100.0%
TT		0	100.0%
FL		12	0.0%
TC		1	91.7%
TC		2	83.3%
CC		0	100.0%
CC		0	100.0%
TT		0	100.0%
TC		1	91.7%

TT		0	100.0%
TT		0	100.0%
TC		0	100.0%
TC		0	100.0%
TC		0	100.0%
CC		1	91.7%
TC		1	91.7%
TC		0	100.0%
TC		1	91.7%
TC		0	100.0%
TC		0	100.0%
TC		1	91.7%
CC		0	100.0%
TT		0	100.0%
CC		0	100.0%
CC		1	91.7%
TT		0	100.0%
TC		1	91.7%
CC		0	100.0%
CC		1	91.7%
CC		1	91.7%
TC		0	100.0%
CC		0	100.0%
TC		0	100.0%
CC		0	100.0%
CC		2	83.3%
CC		0	100.0%
TC		0	100.0%
CC		0	100.0%
TC		0	100.0%
TC		1	91.7%
CC		1	91.7%
TC		0	100.0%
TT		1	91.7%
TC		0	100.0%
TC		0	100.0%
CC		0	100.0%
CC		0	100.0%
CC		0	100.0%
CC		1	91.7%
TT		1	91.7%
TT		0	100.0%
TC		0	100.0%
TT		0	100.0%
TT		0	100.0%
CC		0	100.0%
TT		0	100.0%
TT		1	91.7%
TC		0	100.0%
TC		2	83.3%
TC		0	100.0%
TC		2	83.3%
TC		2	83.3%
CC		0	100.0%
TC		1	91.7%
CC		1	91.7%
TC		1	91.7%
TT		0	100.0%

TC		0	100.0%
TT		0	100.0%
TC		0	100.0%
FL		[illegible]	[illegible]
TT		0	100.0%
TC		1	91.7%
TC		0	100.0%
TC		1	91.7%
TC		0	100.0%
CC		0	100.0%
CC		1	91.7%
TT		1	91.7%
TC		0	100.0%
TC		1	91.7%
CC		0	100.0%
TT		1	91.7%
CC		0	100.0%
TT		0	100.0%
CC		4	66.7%
CC		0	100.0%
TT		1	91.7%
TC		0	100.0%
TC		0	100.0%
TT		0	100.0%
FL		[illegible]	[illegible]
TC		0	100.0%
TT		0	100.0%
TT		0	100.0%
CC		0	100.0%
TC		1	91.7%
TC		1	91.7%
FL		[illegible]	[illegible]
TC		1	91.7%
TC		0	100.0%
TC		1	91.7%
TT		0	100.0%
TT		0	100.0%
TT		0	100.0%
TT		0	100.0%
TC		4	66.7%
TC		1	91.7%
TC		0	100.0%
TC		0	100.0%
CC		0	100.0%
TC		0	100.0%
CC		0	100.0%
TC		0	100.0%
CC		0	100.0%
TC		0	100.0%
CC		0	100.0%
TT		0	100.0%
TC		1	91.7%
TC		1	91.7%
TT		1	91.7%
TT		0	100.0%
TT		0	100.0%
TT		0	100.0%
TT		1	91.7%

TC		0	100.0%
CC		0	100.0%
TC		0	100.0%
TT		0	100.0%
TT		1	91.7%
TC		0	100.0%
CC		0	100.0%
CC		0	100.0%
TC		0	100.0%
TC		0	100.0%
TC		1	91.7%
CC		1	91.7%
TC		0	100.0%
TT		0	100.0%
TC		0	100.0%
TC		0	100.0%
FL		[illegible]	[illegible]
CC		1	91.7%
TC		1	91.7%
CC		1	91.7%
TC		1	91.7%
TT		0	100.0%
TC		2	83.3%
TT		0	100.0%
TC		1	91.7%
TT		0	100.0%
TC		0	100.0%
CC		1	91.7%
TC		0	100.0%
TT		2	83.3%
TT		1	91.7%
TC		1	91.7%
CC		0	100.0%
TC		0	100.0%
TT		0	100.0%
CC		0	100.0%
TC		0	100.0%
TC		0	100.0%
CC		0	100.0%
CC		0	100.0%
TT		0	100.0%
CC		1	91.7%
TT		0	100.0%
TC		0	100.0%
TC		0	100.0%
CC		1	91.7%
TT		1	91.7%
TC		0	100.0%
CC		1	91.7%
TC		0	100.0%
TC		0	100.0%
TT		1	91.7%
TT		0	100.0%
TT		1	91.7%
CC		1	91.7%
TC		1	91.7%

PCT/CA 2005/000250
06 DECEMBER 2005 06-12-05

FL	0	100.0%
TC	0	100.0%
TT	0	100.0%
TT	0	100.0%
TC	0	100.0%
TT	0	100.0%
TC	0	100.0%
TT	0	100.0%
TC	1	91.7%
TC	0	100.0%
TC	0	100.0%
TC	0	100.0%
FL	0	100.0%
FL	1	91.7%
TT	1	91.7%
TT	1	91.7%
TC	1	91.7%
TC	0	100.0%
TC	0	100.0%
TC	0	100.0%
CC	0	100.0%
TC	0	100.0%
TC	2	83.3%
CC	1	91.7%
CC	1	91.7%
TC	1	91.7%
TC	0	100.0%
TC	1	91.7%
CC	0	100.0%
CC	1	91.7%
TC	0	100.0%
TT	0	100.0%
TC	0	100.0%
TC	0	100.0%
CC	0	100.0%
TC	0	100.0%
TT	0	100.0%
TC	0	100.0%
TT	2	83.3%
CC	0	100.0%
CC	0	100.0%
CC	0	100.0%
TC	1	91.7%
TC	0	100.0%
TC	0	100.0%
TC	0	100.0%
TT	0	100.0%
TC	1	91.7%
CC	3	75.0%
TC	0	100.0%
TC	2	83.3%
CC	0	100.0%
TC	0	100.0%

PCT/CA 2005/000250
06 DECEMBER 2005 06-12.05

TC	0	100.0%
TT	0	100.0%
TC	0	100.0%
CC	0	100.0%
TC	0	100.0%
FL	12	0.0%
FL	1	91.7%
CC	1	91.7%
TT	0	100.0%
CC	0	100.0%
CC	1	91.7%
TC	0	100.0%
CC	0	100.0%
TT	0	100.0%
FL	12	0.0%
CC	0	100.0%
TC	0	100.0%
TT	0	100.0%
CC	0	100.0%
TC	0	100.0%
CC	0	100.0%
TT	1	91.7%
TT	0	100.0%
TT	0	100.0%
TC	0	100.0%
TT	1	91.7%
TC	0	100.0%
TC	0	100.0%
TC	1	91.7%
TC	0	100.0%
CC	0	100.0%
CC	0	100.0%
TT	0	100.0%
TC	0	100.0%
CC	0	100.0%
TC	0	100.0%
TT	0	100.0%
TC	6	50.0%
FL	12	0.0%
TT	0	100.0%
FL	12	0.0%
FL	12	0.0%
FL	12	0.0%
FL	12	0.0%

17
355
95.43%
87
178
90
49.58%
50.42%

AMENDED SHEET

CLAIMS

1. A nucleic acid sequence according to any one of the sequences in Table 1 for use in a PCR primer pair for multiplex SNP analysis of a plurality of blood group- or platelet antigen SNPs simultaneously.

2. A set of oligonucleotides comprising at least one primer set of Table 1, wherein said set of oligonucleotides is suitable for amplifying and detecting a plurality of blood group or HPA SNPs simultaneously in a single tube.

3. A nucleic acid sequence according to any one of the sequences in Table 2.

4. A nucleic acid sequence according to claim 3 for use as extension probes for the identification of SNPs.

5. A nucleic acid sequence according to claim 1 or 4, wherein said SNPs relate to blood group and platelet antigens.

6. An oligonucleotide set according to claim 2, wherein said at least one oligonucleotide hybridizes a HPA-1 GP3A SNP for the determination of the HPA genotype and corresponding phenotype.

7. An oligonucleotide primer and probe set for analyzing a plurality of SNPs corresponding to a blood group or platelet antigen genotype, simultaneously; wherein said plurality of SNPs are selected from the group consisting of RhD RHD Exon 4 C/T; RhD RHD Exon 9 A/G; RhC/c RHCE Exon 2 T/C; RhE/e RHCE Exon 5 C/G; S/s GYPB Exon 4 T/C; K/k KEL

Exon 6 T/C; Kp^a/Kp^b KEL Exon 8 T/C; FY/FY0 FY Promoter T/C; Fy^a/Fy^b FY Exon 2 G/A; Jk^a/Jk^b KIDDExon 9 G/A; Di^a/Di^b DIEGO Exon 19 T/C; and HPA-1a/b GP3A Exon 3 T/C.

8. An oligonucleotide primer and probe set for analyzing the SNPs of claim 7, wherein one, more than one or all of said primer set is selected from Table 1, and wherein one, more than one of all of said probe set is selected from Table 2, such that the selection of primer and probe combinations correspond to the SNP being analyzed.

9. A method of simultaneously analyzing a plurality of blood group or platelet antigens in a sample wherein said method comprises:

(a) isolation and purification of genomic DNA from said sample;

(b) multiplex PCR amplification of DNA regions encompassing a plurality of SNPs of interest, each corresponding to a blood group or platelet antigen genotype;

(c) digestion of multiplex PCR amplified products with restriction enzymes;

(d) identification of SNPs using single-base pair primer extension of the amplified DNA fragments using the probes of Table 2;

(e) hybridization of extension products; and

(f) analysis of SNP extension products to determine a genotype corresponding thereto.

10. A method according to claim 9, wherein said restriction enzymes are Exonuclease I and Shrimp alkaline phosphatase for the purpose of removing excess dNTPs and/or oligonucleotides.

11. A method according to claim 9, wherein said extension products are hybridized to tag-arrayed microplate.

12. A method according to claim 9, wherein the multiplex PCR amplification comprises amplification with nucleotides primer and probes selected from Tables 1 and 2.

13. A method according to claim 9, wherein a thermal cylcer is used to carry out the single-pair primer extension.

14. A method according to claim 9, wherein any machine or method capable of analyzing SNPs may be used.

15. A method according to claim 9, wherein GenomeLab SNPstream (Beckman Coulter Inc.) is used to analyze SNP extension products.

16. A method of claim 9, wherein said method is carried out in a single reaction tube or single well of a multiwell plate.

17. A method of claim 9, wherein said method is automated.

18. A method according to claim 9, wherein said antigens are red blood cell and platelet blood group antigens.

19. A method according to claim 9, wherein said antigens are selected from the group consisting of

ABO, Rh (D, C, c, E, e), MNS, P, Lutheran, Kell (K, k), Lewis, Duffy (Fy^a, Fy^b), Kidd (Jk^a, Jk^b).

20. A method for the simultaneous detection of the presence or absence of blood cell antigen SNPs simultaneously using one or more of the the oligonucleotides of Table 1 and Table 2, or any corresponding combination thereof.

21. A method according to any one of claims 9 to 20, wherein 12 blood group and HPA SNPs are analyzed in a single tube.

22. A method according to claim 9, wherein said SNPs identified in step (d) include a HPA-1 GP3A SNP which is analyzed for the determination of HPA genotype and corresponding phenotype.

23. A multiplex PCR method for the identification of blood group genotypes, comprising identifying and analyzing the corresponding SNPs combinations thereof according to the following steps:

(a) isolation and purification of genomic DNA from said sample;

(b) multiplex PCR amplification of DNA regions encompassing said plurality of blood group SNPs, and including a plurality of primer pairs of Table 1;

(c) the digestion of multiplex PCR amplified products with restriction enzymes;

(d) identification of SNPs using single-base pair primer extension of the amplified DNA fragments;

(e) hybridization of extension products; and

(f) analysis of SNP extension products to determine the SNP genotype; wherein said analysis simultaneously screens a plurality of SNPs in a single reaction tube.

24. A method according to claim 14, wherein said test sample is a human blood sample.

25. A method according to claim 14, wherein said plurality of SNPs are selected from the group consisting of RhD RHD Exon 4 C/T; RhD RHD Exon 9 A/G; RhC/c RHCE Exon 2 T/C; RhE/e RHCE Exon 5 C/G; S/s GYPB Exon 4 T/C; K/k KEL Exon 6 T/C; Kp^a/Kp^b KEL Exon 8 T/C; FY/FY0 FY Promoter T/C; Fy^a/Fy^b FY Exon 2 G/A; Jk^a/Jk^b KIDDExon 9 G/A; Di^a/Di^b DIEGO Exon 19 T/C; and HPA-1a/b GP3A Exon 3 T/C.

26. The use of nucleic acid sequences of Tables 1 and 2 in multiplex PCR for the identification and analysis of blood group or platelet antigen SNPs.

27. The use according to claim 26, wherein said multiplex PCR is carried out in a single reaction tube.

28. The use according to claim 26, wherein said multiplex PCR is automated to simultaneously analyse blood group and platelet antigen SNPs.

29. The use according to claim 26, wherein said SNP analysis results in antigen genotypes and corresponding phenotypes of a test sample.

30. A method of claim 23 wherein blood group antigen and platelet antigen typing is determined using the primer pairs of Table 1, and analysis using the probes of Table 2.

31. A method of claim 30, wherein said typing uses a multiplex PCR SNP analysis format, wherein said analysis is automated.

32. A method of simultaneously analyzing a plurality of blood group or platelet antigens in a sample wherein said method comprises:

(a) isolation and purification of genomic DNA from said sample;

(b) multiplex PCR amplification of DNA regions encompassing a plurality of SNPs of interest, using a plurality of primer pairs of Table 1;

(c) digestion of multiplex PCR amplified products with restriction enzymes;

(d) identification of SNPs using single-base pair primer extension of the amplified DNA fragments using probes corresponding to said SNPs of interest;

(e) hybridization of extension products; and

(f) analysis of SNP extension products to determine the SNP genotype.

33. The method of claim 23, wherein said step of identification of SNPs includes using the probes of Table 2.

34. The method of claim 23, wherein said step of hybridization includes using the probes of Table 2.

35. The method of claim 23, wherein said blood group SNPs includes a SNP of Table 1 or Table 1A.

36. The method of claim 30 wherein said blood group antigen and platelet antigen are human antigens.